Fever in melanoma: new drugs or bugs?

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Sir,

Cancer treatment is being revolutionized through the use of targeted and immunotherapy-based treatments. Infectious diseases clinicians have traditionally associated cancer therapy with infectious complications as a result of immunosuppressive effects; however, many novel treatments have immunomodulatory effects that may mimic infectious diseases. BRAF and mitogen-activated protein kinase kinase (MEK) inhibitors (e.g. dabrafenib (DAB), ± trametinib (TRAM)) are molecular therapies used for the treatment of advanced melanoma that are also being trialled in other tumours including papillary thyroid cancer, colorectal cancer and ovarian cancer. Fever is a frequent complication of BRAF and MEK inhibitors [1,2]. Infectious diseases clinicians are therefore increasingly likely to consult on such patients and need to be aware of the toxicities of these agents to avoid unnecessary investigations and antimicrobial use. Because of this, we reviewed all patients with advanced melanoma treated with DAB/TRAM in our centre over a 4-year period (2011–15) to determine the frequency and nature of DAB/TRAM reactions.

All patients that had received DAB/TRAM for advanced melanoma at the Austin Hospital, Melbourne, Australia were identified through pharmacy records and their medical records were retrospectively analysed. Patients received either DAB alone at a dose of 150 mg twice-daily or combination therapy with DAB 150 mg twice-daily and TRAM 2 mg daily. Patients undergoing clinical trials were included in the analysis.

Data collected included patient demographics, details regarding febrile episodes (cause, clinical features, management (hospitalization, investigations, treatment discontinuation and steroid use)) and clinical outcomes. Febrile episodes were defined as any fever $\geq$38.0°C, with potential causes for the fever defined as either due to infection or DAB/TRAM (DAB/TRAM-related febrile episode (DTFE)) if no alternative cause was found. Occurrence of pyrexial symptoms (e.g. chills, myalgias, sweats) without fever was not considered an episode. Other definitions used were as follows: tachycardia (heart rate >100 beats/min); hypotension (systolic blood pressure <90 mmHg, or decrease in systolic blood pressure >40 mmHg); and resolution of febrile episode (24-h period of temperature $\leq$37.5°C).

Approval was obtained from the Austin Health Human Research and Ethics Committee to undertake the study. Statistical analysis was performed using STATA/IC 12.1 (StataCorp, College Station, TX, USA). Fisher's exact test and chi-squared test were used to compare categorical variables, as appropriate.

Thirty-three patients (median age 58 years, range 34–85 years; 23 (70%) male) received DAB/TRAM therapy (28 DAB/TRAM, five DAB alone) for a total of 321.1 patient-months. There were 41 febrile episodes in 18/33 (55%) patients. DTFE accounted for 38 (88%) episodes and only 3 (12%) were due to infection. Patients had a mean of 2.2 DTFE (range 1–5) that occurred a median of 36 days (mean ± SD 50 ± 45 days, range 2–146 days) after commencement of treatment or a median of 28 days (mean ± SD 62 ± 59 days, range 4–180 days) after re-commencement of treatment.

The clinical characteristics of DTFE are summarized in Table 1. Factors associated with DTFE included rigors (13/38 (34%) episodes, 7/33 (21%) patients) and rash (7/38 episodes (8%); 3/33 (9%) patients), while hypotension (2/38 episodes (5%), 2/33 (6%) patients) and neutrophilia (1/30 (3%) episodes, 1/33 (3%) patients) were uncommon. There were no localizing features in any DTFE. Mean C-reactive protein during episodes was 78 ± 47 mg/L (range 1.5–166 mg/L). Among the three episodes of infection-associated febrile episodes (upper respiratory tract infection, hospital-acquired pneumonia and empyema), localizing features (3/3 (100%), p <0.0001), hypotension (2/3 (66%), p 0.021), tachycardia (2/3 (66%), p 0.035) and a C-reactive protein > 200 mg/L (2/3 (66%), p 0.0037) were all more common than for DTFE. Of the three patients who had infection-associated febrile episodes, two also had DTFE and 2/3 (67%) died due to their infection.

Management of DTFE is summarized in Table 1. Patients were hospitalized in 14/38 episodes (37%) for a median of 4 days (range 2–12 days). Antimicrobials were administered empirically in 11/38 episodes (29%; vancomycin, 1; piperacillin/tazobactam, 2; ceftriaxone, 5; flucloxacillin, 4; cephazolin/cephalexin, 2;

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TABLE 1. Clinical features and management of febrile episodes (n = 38) linked to debrafenib and trametinib use in advanced melanoma

Feature	Total (*n* = 38)
Clinical features of febrile episodes	
Mean of maximum temperatures during febrile episodes	39.1°C (range 38.1–41°C)
Rigors	13 (34%)
Tachycardia	3 (8%)
Hypotension	2 (5%)
Skin rash	7 (18%)
Localizing symptoms	0 (0%)
C-reactive protein – mean ± SD (range)	78 ± 47 mg/L (range 1.5–166 mg/L)
Neutrophil count – mean ± SD (range)	$4.4 \times 10^9 \pm 2.3 \times 10^9$ cells/L (range 1.1×10^9 to 12.7×10^9 cells/L)
Management and outcomes of febrile episodes	
Hospitalization	14 (37%)
Median duration of hospitalization	4 days (range 2–12 days)
Empirical antibiotic use	11 (29%)
Median time to resolution of fever	2 days (range 1–17 days)
Melanoma treatment interruption	24 (63%)
Median treatment interruption duration	2.5 days (range 1–13 days)
Received corticosteroid therapy	15 (39%)
Median prednisolone dose used	20 mg (range 5–25 mg)
Corticosteroids given as 'secondary prophylaxis'	13 (34%)
Median prednisolone dose used as secondary prophylaxis	10 mg (range 5–30 mg)

amoxicillin/clavulanic acid, 1; azithromycin/doxycycline, 4) for a total of 80 days. Melanoma treatment interruption occurred in 24/38 (63%) episodes and corticosteroids were given in 15/38 (39%) episodes. Fevers resolved after a median of 3 days (range 1–17 days) for episodes where treatment was discontinued. In 13/38 (34%) episodes patients continued to receive corticosteroids as 'secondary prophylaxis' for fevers. Of patients that did not have DTFE, 9/16 (56%) were receiving corticosteroids as symptomatic treatment of metastases.

Although febrile reactions have previously been reported with BRAF/MEK inhibitor therapy, the relative frequency (55% patients) and clinical characteristics of these reactions have not been accurately defined. In fact, DTFE was by far the most common (93%) reason for febrile episodes in these patients, who typically had no localizing features (100%), but rigors (34%) and occasionally rash (8%), together with only a modest rise in C-reactive protein; without signs of sepsis such as hypotension or neutrophilia. This clinical clustering has not been fully appreciated previously [1–5], despite its likely utility for clinicians faced with a febrile patient with melanoma. Importantly, DTFE appear to be short-lived with rapid resolution of fevers following discontinuation of treatment and respond well to moderate-dose corticosteroid treatment. Persistence of fevers beyond 4 days despite these measures helps to exclude BRAF/MEK inhibitors as a cause of fever. Frustratingly, the pathogenesis of fever due to BRAF/MEK inhibitor therapy remains unclear [4].

This study had some limitations. First, due to its retrospective nature there was no standard approach to the management of fevers, so making it difficult to assess the relative contributions of melanoma treatment interruption and use of corticosteroids. Second, there were (interestingly) few episodes of infection-related fevers in our study population, making direct comparison with DTFE less definitive. Finally, as BRAF/MEK inhibitors are now being used for other non-melanoma solid tumours, we cannot be certain that the same pattern of febrile reactions will occur in such settings.

Clinicians need to be increasingly aware of the adverse effects of BRAF/MEK inhibitor therapy for melanoma, such that while a thorough work-up for infectious causes will almost always be required, unnecessary excess hospitalization and empiric antibiotic therapy can be minimized.

Conflict of interest

All authors have stated that there are no conflicts of interest.

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